



# Cancer Research Center Hotline

## Lung Cancer Treatment Present and Future

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Lung cancer is the most lethal cancer afflicting men and women. In the United States, during 2002, over 169,000 new cases of lung cancer will have been diagnosed with all but 14% dying of their disease in 5 years. The 154,000 lung cancer deaths anticipated during 2002 will exceed the combined deaths from breast, prostate, and colorectal cancer.<sup>1</sup>

There are two major types of lung cancer. The more common, non-small cell lung cancer (NSCLC) accounts for 75-85% of all lung cancers, with small cell lung cancer (SCLC) comprising the majority of the remaining 15-25%. Besides the histological differences, there are distinct molecular, biological, and clinical characteristics that set them apart. An accurate histological diagnosis is imperative, since different treatment strategies may be used for each type of lung cancer.

Despite the high prevalence and deadly nature of the disease, research in lung cancer has lagged behind research in other common malignancies. There is still a lack of screening and early detection methods to identify patients with more curable disease. More importantly, despite treating the disease at the earliest stages, death from lung cancer nearly always results from the development of metastases.

### Small Cell Lung Cancer

The treatment for SCLC differs from NSCLC. Surgery is rarely used, and instead the primary treatment modalities are cytotoxic chemotherapy and/or radiotherapy. The treatment and prognosis are stage dependent. When the disease is confined to one hemithorax excluding an ipsilateral malignant pleural effusion (limited stage), the combined use of platinum-based chemotherapy and radiotherapy administered either concurrently or sequentially offers the greatest chance for long-term survival and cure. Overall response rates of 65-85% with complete response rates of 45-75% can be predicted and translate into a median survival of 18-24 months with 2-year and 5-year survival rates of 40% and 20% respectively.<sup>2</sup>

When the disease has spread beyond one hemithorax and/or associated with a malignant pleural effusion (extensive stage), treatment is primarily platinum-based chemotherapy. Overall response of 50-60% with complete response rates of 20-30% can be predicted, which translates into a median survival of 8-9 months and a 2-year survival of <10%. In extensive stage SCLC, radiotherapy is only commonly administered for palliation.<sup>2</sup>

Major improvements in the treatment of SCLC have been few in

the last decade. One recently completed Phase III trial from Japan reported superior response and survival rates when a new agent, irinotecan, is substituted for etoposide in combination with cisplatin in extensive stage SCLC.<sup>3</sup> A similar study is presently being conducted in the U.S. with the intent to see if the results can be duplicated.

### Non-Small Cell Lung Cancer

The treatment and prognosis of NSCLC is dependent on the stage of the disease at diagnosis. Considered the most curative form of treatment for NSCLC, surgery is the primary therapy for localized disease. For Stage I and II NSCLC (disease that has not spread beyond hilar lymph nodes), surgical treatment results in a 5-year survival of 55-65% and 30-35% respectively.

Patients who are inoperable due to medical reasons or decline surgery may be treated with definitive radiotherapy but with inferior survival rates compared to surgery. Presently there is no consistent data that show that post-operative (adjuvant) radiotherapy and/or cytotoxic chemotherapy improves survival in localized NSCLC.

The treatment for more advanced loco-regional disease (Stage IIIA), where the tumor has spread to the ipsilateral mediastinal lymph nodes, usually involves surgery and radiotherapy or the combination of surgery, radiotherapy, and cytotoxic chemotherapy. The 5-year survival rate for Stage IIIA disease is 20-25%. When the disease extends to involve major mediastinal structures such as the trachea, great vessels, supraclavicular lymph nodes, or is associated with a malignant pleural effusion (Stage IIIB), treatment is limited to radiotherapy and/or cytotoxic chemotherapy. The 5-year survival for this stage of disease is <10%.

When metastases are present (Stage IV), the cornerstone of treatment is cytotoxic chemotherapy. The 5-year survival for Stage IV NSCLC is a dismal <1%. Several general statements may be made regarding the role of chemotherapy in the treatment of advanced NSCLC (Stage IIIB, IV): 1) Cytotoxic chemotherapy leads to symptomatic improvement and longer survival.<sup>4</sup> 2) The use of platinum-based (cisplatin, carboplatin) combination chemotherapy results in superior response and survival rates compared to single drug therapy. 3) Combination regimens incorporating newer drugs such as gemcitabine, paclitaxel, irinotecan, docetaxel, and vinorelbine result in superior response and survival rates (median survival 8-9 months; 1-year survival approximately 35%) compared to older regimens. 4) Second-line chemotherapy with docetaxel improves survival compared to supportive care only.<sup>5</sup>

Despite improvements in drug therapy, the benefits of chemotherapy may have reached a plateau. A recently reported Phase III trial, comparing four commonly used combination chemotherapy regimens for advanced NSCLC failed to show a superiority of any one regimen, adding support to such a conclusion.<sup>6</sup>

### Newer Approaches to the Treatment of Lung Cancer

The treatment of lung cancer is less than optimal. Modest benefits are achievable with present-day treatments for early lung cancer but much more difficult to obtain in advanced disease. With advances in molecular biology, genetics, pharmacology, pathology, and biotechnology, the focus has shifted to developing treatments directed at specific targets in or on the tumor cell. The goal is to disrupt

certain unique properties of neoplastic cells such as proliferation, angiogenesis, anti-apoptosis, invasion and the ability to metastasize. The following is a brief synopsis of three agents that are the farthest along in development. They all interfere with the function of an important growth factor found in normal and neoplastic tissue: the epidermal growth factor receptor.

The epidermal growth factor receptor (EGFR) is a member of the epidermal growth factor family made up of four similar receptor tyrosine kinase proteins, EGFR (Erb-1,HER-1), HER-2/neu (Erb-2), HER-3 (Erb-3), and HER-4 (Erb-4). They are transmembrane 170-kd glycoproteins that mediate cell proliferation, differentiation, and survival. EGFR consists of an extracellular ligand-binding domain, a transmembrane region and a cytoplasmic protein kinase domain. Upon ligand binding, a series of intracellular signaling pathways are triggered, which lead to cell proliferation, increased angiogenesis, loss of normal apoptosis, and increased metastatic potential. EGFR is frequently over expressed in NSCLC and rarely in SCLC.<sup>7</sup>

### Gefitinib

Gefitinib (ZD1839, Iressa[Astra – Zeneca]) is a potent EGFR tyrosine kinase inhibitor (TKI). Of the new agents directed at novel targets of lung cancer, the most clinical experience has been with gefitinib.

Two large Phase II trials have been reported and have shown that this agent indeed has activity in advanced NSCLC. Response rates varied from 9-19% depending on the trial. More importantly, 35-43% of patients experienced an improvement in disease-related symptoms. Major toxicities were diarrhea and an acneiform rash. There was no significant myelosuppression or hair loss.<sup>8,9</sup>

Based on these results, two Phase III trials in NSCLC comparing gefitinib in combination with chemotherapy to chemotherapy alone were started and were rapidly completed.<sup>10,11</sup> Disappointingly, no improvement in survival has been demonstrated in either trial with the addition of gefitinib. Clinical trials are continuing with gefitinib in combination with various chemotherapy agents given concurrently or sequentially.

### Erlotinib

Erlotinib(OSI774,Tarceva[Genentech]) is a EGFR tyrosine kinase inhibitor structurally similar to gefitinib. Phase I trials found this agent to be well tolerated with the principal toxicities being diarrhea and skin rash similar to gefitinib. A Phase II trial of 56 patients with recurrent or progressive NSCLC resulted in a disease control rate of 45%.<sup>12</sup>

Two Phase III trials in NSCLC evaluating erlotinib in combination with chemotherapy have been completed, but results are not available. Another Phase III trial evaluating erlotinib as monotherapy in previously treated patients with advanced NSCLC is ongoing.

### Cetuximab

Cetuximab (C-225, Erbitux [Imclone]) is a human chimeric monoclonal antibody that binds to the EGFR with high affinity, comparable to the natural ligand. It causes down regulation of the EGFR by competing with ligand binding. In the Phase I trials, the drug appeared to be well tolerated with the principal toxicities being asthenia, fever, chills, skin rash and allergic reactions. Phase I/II

trials are ongoing to evaluate cetuximab as first line therapy in combination with chemotherapy and as salvage treatment with chemotherapy.<sup>13</sup>

The above-mentioned drugs are but a few of the many targeted therapies for lung cancer. Up to now nearly all of them have been directed at NSCLC. Other targeted therapies being evaluated in clinical trials include Ras/farnesyl transferase inhibitors, pro-apoptotic agents, inhibitors of angiogenesis, and vaccines.

### Conclusion

Lung cancer remains a major health problem. Early detection methods so far have proven inadequate and treatment even when the disease is diagnosed early remains suboptimal. Identification of a number of novel targets of lung cancer has led to the development of targeted therapies with fewer side effects and in selected clinical situations equal efficacy when compared to conventional chemotherapy. It is likely that with the development of such agents that we will see a change in the treatment paradigm for lung cancer. Many questions remain unanswered in terms of the exact role these newer treatments will play in lung cancer management. A concerted effort by all disciplines involved in the study and treatment of this disease will be needed to answer these questions. *Research Brings Hope.* For more information visit the Cancer Research Center's website at [www.crch.org](http://www.crch.org) or call the Cancer Information Service of Hawaii at 1-800-4-CANCER.

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